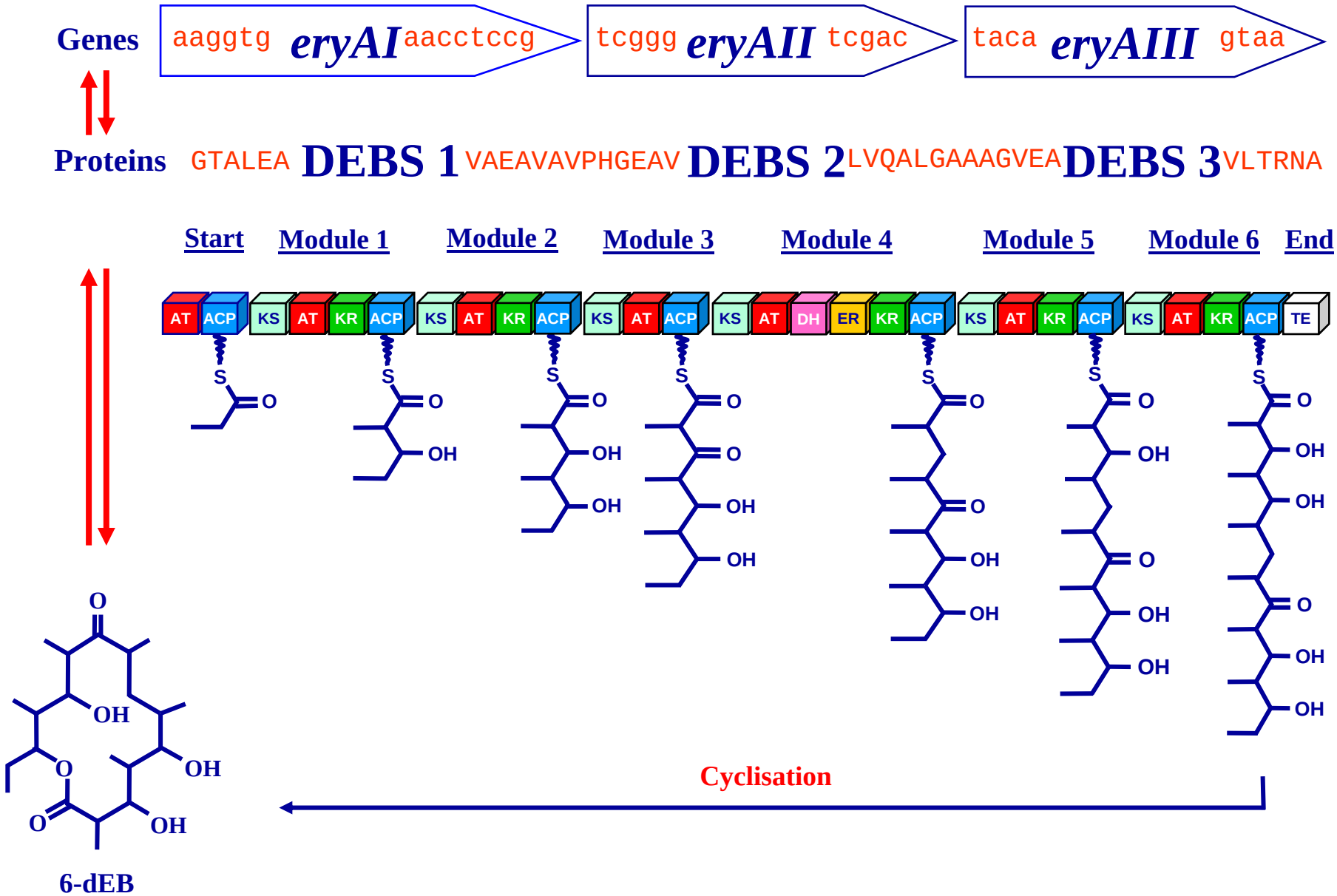
Why the *in silico* Drug Design and Discovery

FACULTY OF FOOD TECHNOLOGY AND BIOTECHNOLOGY
PBF
UNIVERSITY OF ZAGREB - CROATIA
1956

and Novalis

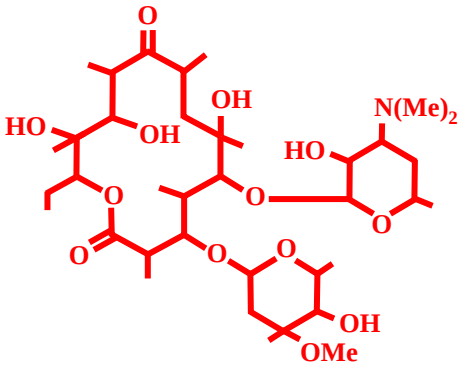
Daslav Hranueli

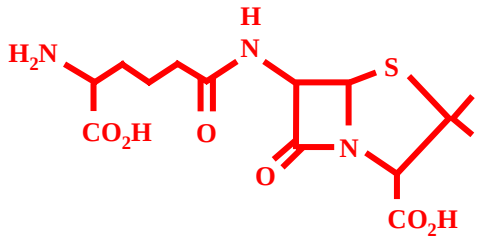
Modular type I PKS, e.g. erythromycin:



Biological activity of polyketides and peptides:

Erythromycin A





Isopenicillin N

50% of most important medications:

- **not only**

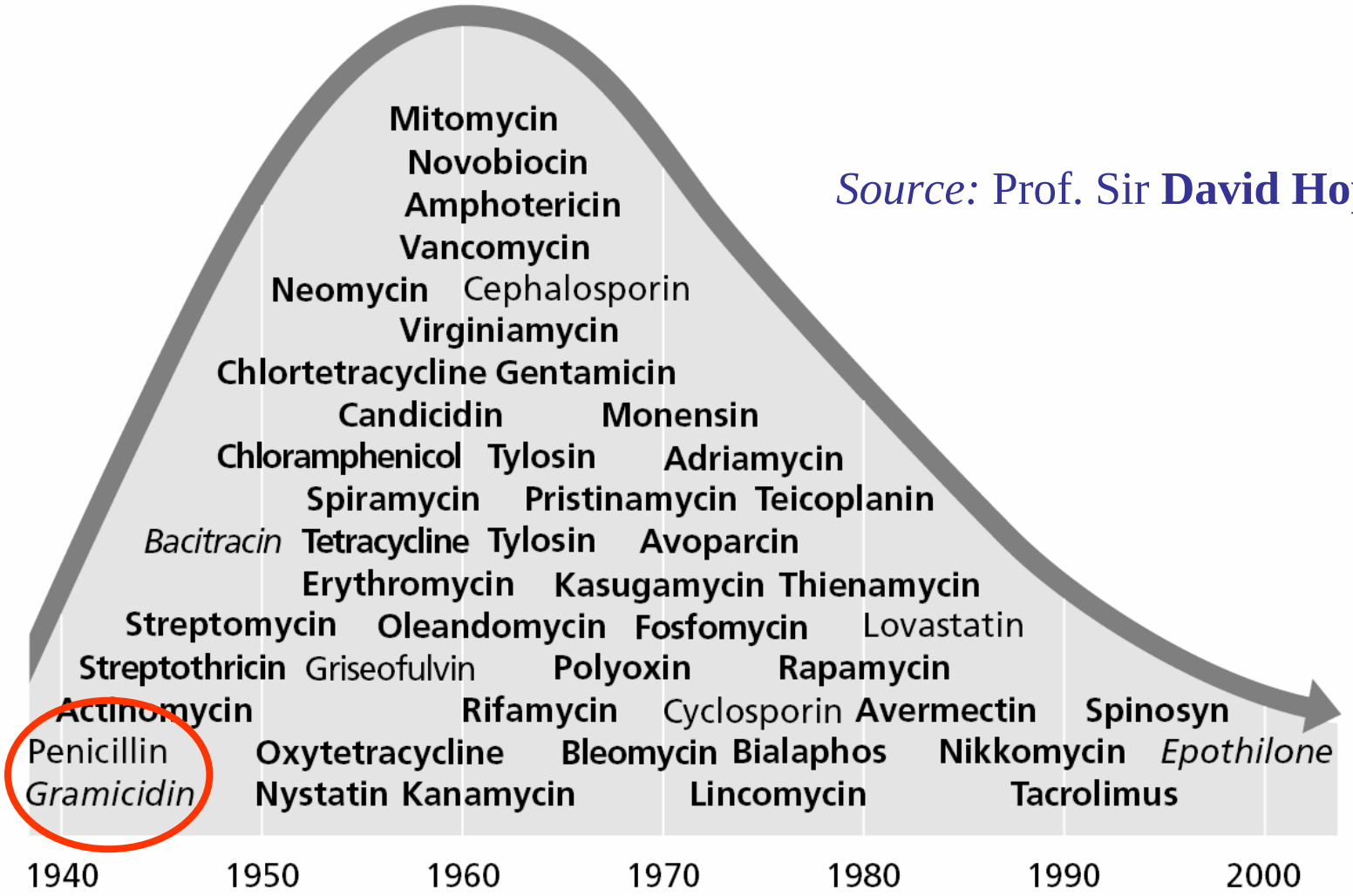
  antibacterials,
  antifungals,
  antivirals, and
  antitumor compounds

- **but also products with**

  immunosuppressants,
  antihypertensives,
  antidiabetics,
  antimalarials, and
  antiholesterolemics

(**Hranueli** *et al*., *Curr. Med. Chem.*, ***12***, 1697, 2005)

Biological activity of polyketides and peptides:



Source: Prof. Sir **David Hopwood**

Are there more Actinomycetes to be discovered?

- **New Species - PubMed search:**

  "Actinomycete sp. nov." (30/05/08)

  - 2006 – **40**
  - 2007 – **38**
  - 2008 – **18**

- **New Genera - PubMed search:**

  "Actinomycete gen. nov. sp. nov." (30/05/08)

  - 2006 – **7**
  - 2007 – **4**
  - 2008 – **2**

(**Richard Baltz**, *Cubist Pharmaceuticals, Inc., USA*
Natural products discovery & Production II,Whistler, British Columbia, Canada, 2008)

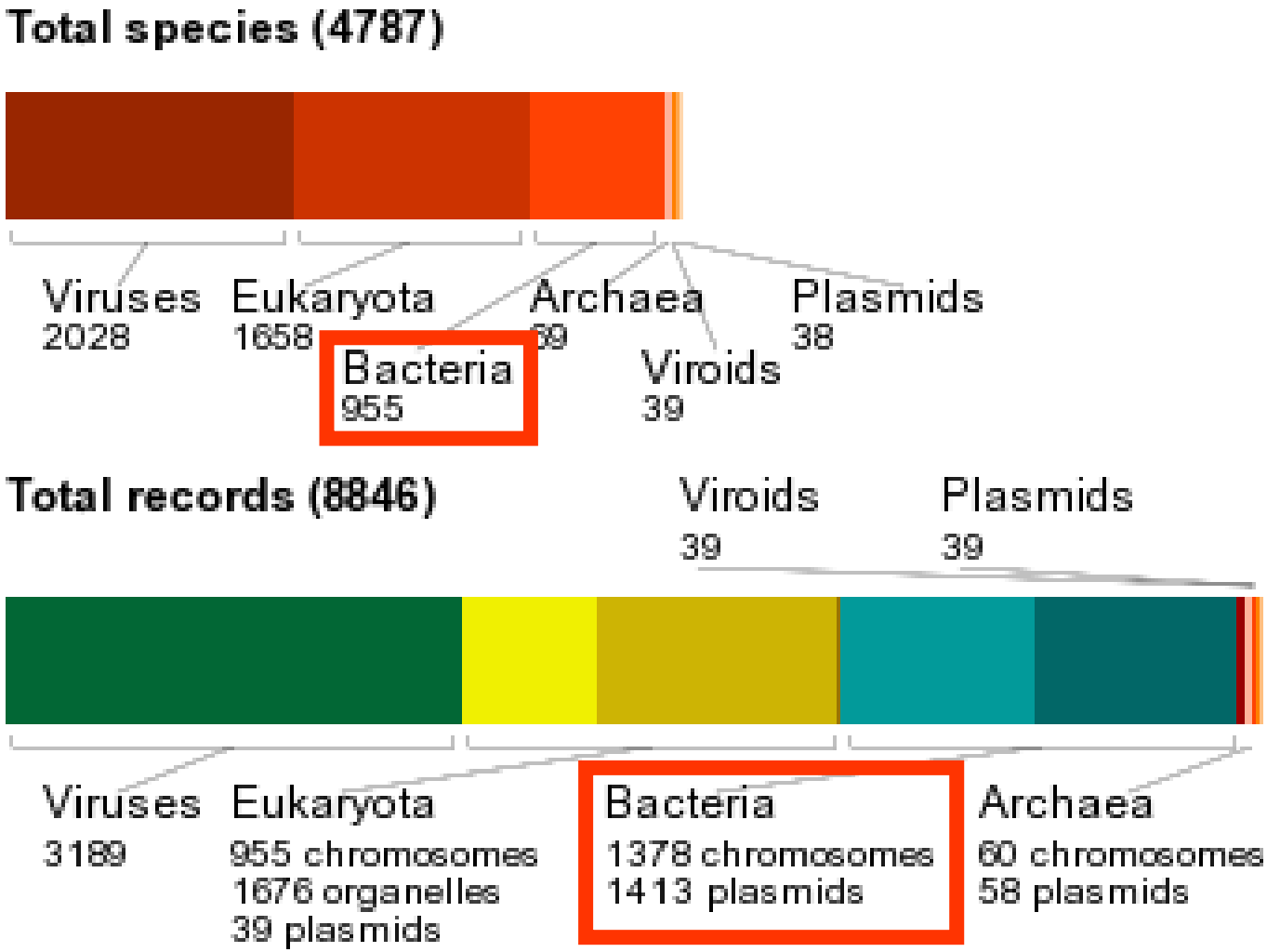
Biological activity of polyketides and peptides:

Alternative strategies

to explore chemical potential

of natural products?

Current Status of Genome Sequencing Projects NCBI (16/10/2008)



PKS and NRPS gene-clusters in bacteria:

Species	Size (MB)	PKS/NRPS (KB)
Zymomonas mobilis	2.0	0
Gluconobacter oxydans	2.9	0
Clostridium perfringens	3.1	0
Brucella abortis	3.3	3
Corynebacterium glutamicum	3.3	0
Bacillus licheniformis	4.2	35
Escherichia coli K12	4.7	5.5
Xyanthomonas campestris	5.1	4
Salinospora tropica	5.2	516
Photorhabdis luminescens	5.7	208
Pseudomonas aeruginosa	6.3	74
Nocardia farcinica	6.3	204
Pseudomonas fluorescens	7.1	183
Saccharopollyspora erythraea	8.2	410
Streptomyces coelicolor	8.6	135
Streptomyces avermitilis	9.2	356

(**Donadio** *et al.*, *Nat. Prod. Rep.*, ***24***, 1073, 2007)

PKS and NRPS gene-clusters cont':

Secondary metabolite - Mozilla

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Home Bookmarks The Mozilla Organiza... Latest Builds CORDIS FP6: Home ...

EBI Databases Nucleotide for Go Clear

13	polyketide	*pks11*	113361	118594	2	5234
14	polyketide	*pte*	487415	567017	13	79603
15	polyketide	*ave*	1132445	1212360	18	80916
16	polyketide	*pks2*	1895794	1913284	4	17491
17	polyketide	*pks3*	2773878	2784841	7	10964
18	polyketide	*pks5*	2877941	2894413	4	16473
19	polyketide	*pks9*	2897395	2913535	15	16141
20	polyketide	*olm*	3534525	3634593	12	100068
21	polyketide	*pks8*	4527901	4540450	14	12550
22	polyketide	*rpp*	8490207	8492484	2	2278
23	polyketide	*pks4*	8553602	8561604	3	8003
24	polyketide	*pks1*	8776963	8789766	4	12804
				Subtotal	98	362525
25	peptide	*nrps6*	754376	763274	7	8899
26	peptide	*nrps7*	991484	1042269	32	50786
27	peptide	*nrps8*	1549424	1554224	3	4801
28	peptide	*nrps3*	3930088	3938730	6	8643
29	peptide	*nrps1*	3974805	3996189	7	21385
30	peptide	*nrps2*	4494250	4526990	16	32741
31	peptide	*nrps5*	7930737	7937201	4	6465
32	peptide	*nrps4*	8522760	8530697	5	7938
				Subtotal	80	141658

Start Genome P... kongres - ... Kalendar -... Removabl... Secondar... 14:10

Avermectin

Oligomycin

11 PKS gene-clusters

S. coelicolor	2 PKS, 4 NRPS and 2 PKS/NRPS
Sac. erythrea	11 PKS, 6 NRPS and 1 PKS/NRPS
S. griseus	6 PKS, 7 NRPS and 2 PKS/NRPS
S. scabies	3 PKS, 4 NRPS and 1 PKS/NRPS

8 NRPS gene-clusters

Total	33 PKS, 29 NRPS and 6 PKS/NRPS

68 gene-clusters in only 5 genomes

Current Status of Genome Sequencing Projects NCBI (16/10/2008) cont'

Microbial Genome Sequencing Projects in Progress - Microsoft Internet Explorer

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Address http://www.ncbi.nlm.nih.gov/genomes/lproks.cgi Go Links

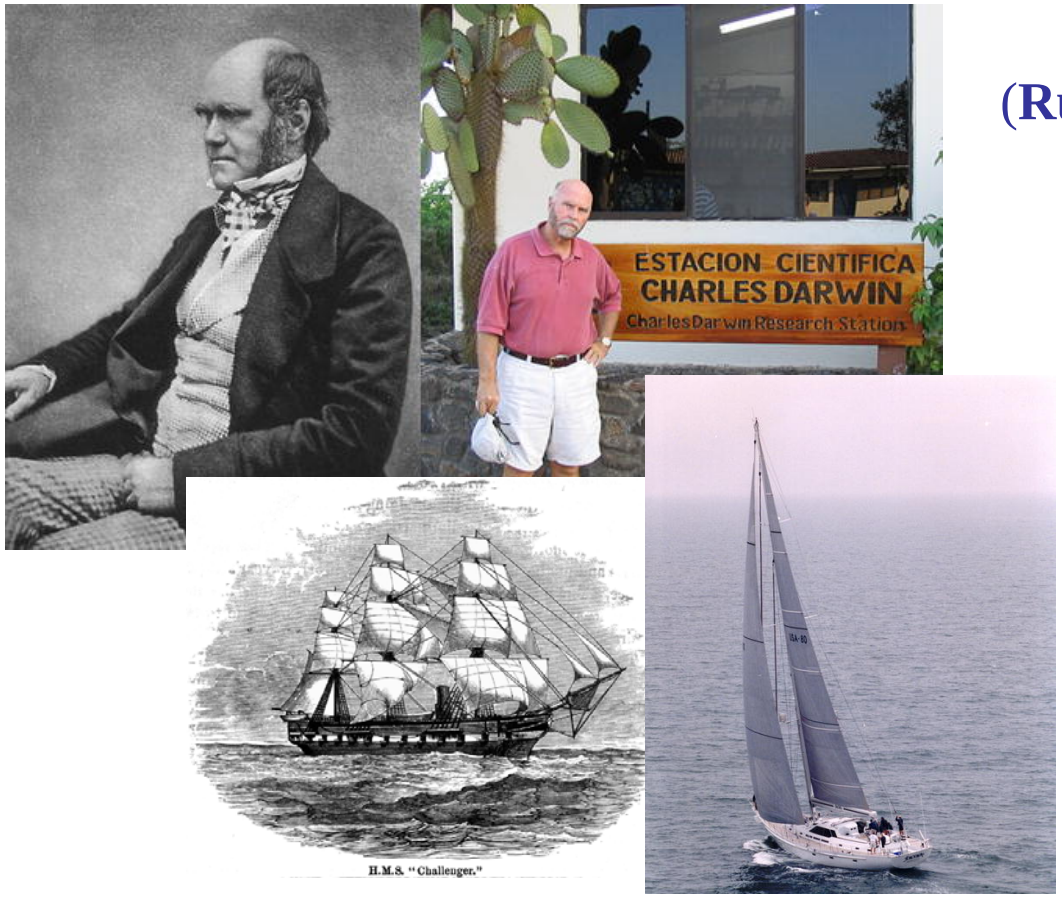
352	Streptococcus suis P1/7	B	Firmicutes	-	-	*1.83	40	-	-	-	Sanger Insti
353	Streptococcus uberis 0140J	B	Firmicutes	-	-	*1.82	40	-	-	-	Sanger Insti
93	Streptomyces ambofaciens ATCC 23877	B	Actinobacteria	-	-	*8	72	-	-	-	Genoscope
19249	Streptomyces clavuligerus ATCC 27064	B	Actinobacteria	-	-	-	-	-	-	-	Korea Resea Institute of Bioscience a Biotechnolo
28551	Streptomyces clavuligerus ATCC 27064	B	Actinobacteria	597	5981	-	71.1	NZ_ABJH00000000	BLAST	02/28/08	Broad Instit
13658	Streptomyces peucetius ATCC 27952	B	Actinobacteria							-	Institute of Biomolucule Reconstruct
28553	Streptomyces pristinaespiralis ATCC 25486	B	Actinobacteria	532	5591	-	70.4	NZ_ABJI00000000	BLAST	02/28/08	Broad Instit
12985	Streptomyces scabiei	B	Actinobacteria	-	-	-	-	-	-	-	Sanger Insti
28547	Streptomyces sp. Mg1	B	Actinobacteria	466	6637	-	71.2	NZ_ABJF00000000	BLAST	02/28/08	Broad Instit
28549	Streptomyces sp. SPB74	B	Actinobacteria	534	4638	-	71.9	NZ_ABJG00000000	BLAST	02/28/08	Broad Instit
28555	Streptomyces sviceus ATCC 29083	B	Actinobacteria	522	7990	-	70.1	NZ_ABJJ00000000	BLAST	02/28/08	Broad Instit
21083	Streptosporangium roseum DSM 43021	B	Actinobacteria	-	-	-	69-71	-	-	-	DOE Joint Genome Inst
18181	Subdoligranulum variabile DSM 15176	B	Firmicutes	-	-	-	52.2	-	-	-	Washington University (WashU)

10 Actinobacteria

PKS and NRPS gene-clusters cont':

Significant chemical diversity potential in sequenced genomes

Sequencing of largest metagenomic dataset:



(**Rusch** *et al.*, *PLoS Biol.* ***5***, e77, 2007)

CAMERA database

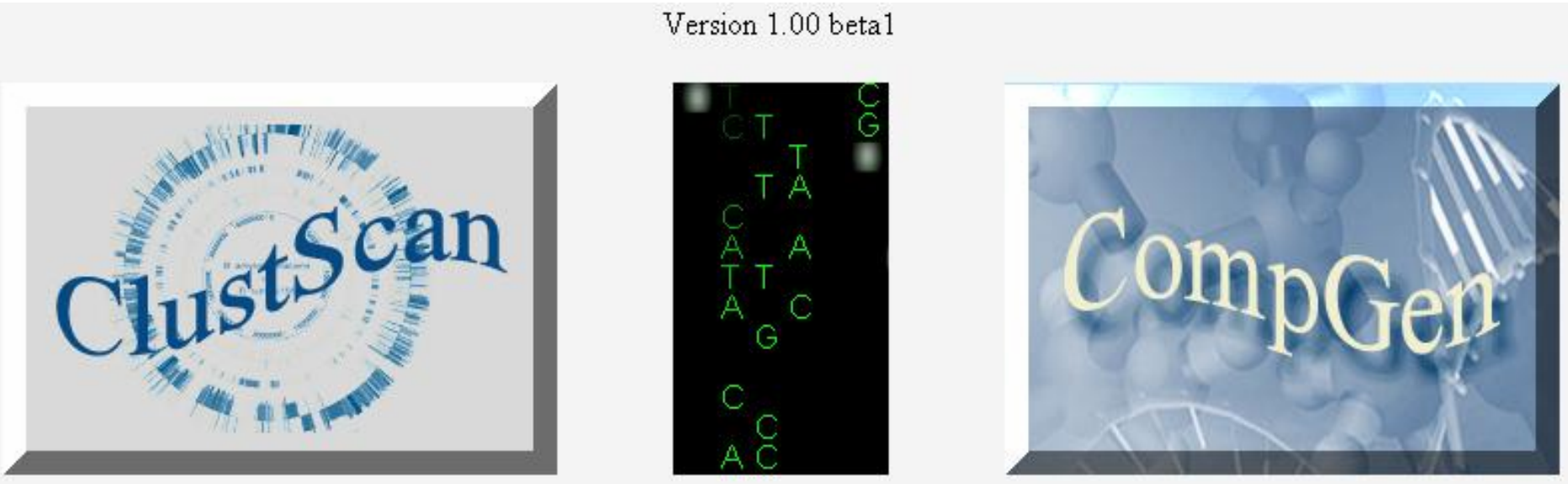
- **7.7 million sequencing reads**
- **6.3 billion bp of DNA**

Sequencing of largest metagenomic dataset:

Computational tools needed for rapid mining of massive DNA datasets to hunt for gene clusters encoding entirely novel compounds

Program packages:

and **Novalis**



***Clust*er *Scan*ner** ***Comp*ound *Gen*erator**

Java and JavaScript; Linux server (http://bioserv.pbf.hr/)

Java client on user's computer